FORM PTO-1390 (REV 10-95) U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. §371

ATTORNEY'S DOCKET NUMBER: BREVA 1

U.S. APPLICATION NO. (If known, see 37 CFR §1.5): 10/069928

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/IB00/01161	23 AUGUST 2000	1 SEPTEMBER 1999

TITLE OF INVENTION: RADIOPHARMECEUTICAL PRODUCTS AND THEIR PREPARATION PROCEDURE

APPLICANT(S) FOR DO/EO/US: BELLANDE,Emmanuel, et al

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ■ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. §371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. §371.
3. ☐ This express request to begin national examination procedures (35 U.S.C. §371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. §371(b) and PCT Articles 22 and 39(1).
4. ■ A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.
5. ■ A copy of the International Application as filed (35 U.S.C. §371(c)(2))
   a. ☐ is transmitted herewith (required only if not transmitted by the International Bureau).
   b. ■ has been transmitted by the International Bureau.
   c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US).
6. ☐ A translation of the International Application into English (35 U.S.C. §371(c)(2)).
7. ■ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. §371(c)(3))
   a. ☐ are transmitted herewith (required only if not transmitted by the International Bureau).
   b. ■ have been transmitted by the International Bureau.
   c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
   d. ■ have not been made and will not be made.
8. ☐ A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. §371(c)(3)).
9. ☐ An oath or declaration of the inventor(s) (35 U.S.C. §371(c)(4)).
10. ☐ A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. §371(c)(5)).

Items 11. to 16. below concern document(s) or information included:

11. ☐ An Information Disclosure Statement under 37 C.F.R. §§1.97 and 1.98.
12. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 C.F.R. §§3.28 and 3.31 is included.
13. ■ A FIRST preliminary amendment.
    ☐ A SECOND or SUBSEQUENT preliminary amendment.
14. ☐ A substitute specification.
15. ☐ A change of power of attorney and/or address letter.
16. ☐ Other items or information:

U.S. APPLICATION NO. (if known, see 37 CFR §1.5)	INTERNATIONAL APPLICATION NO.	ATTORNEY'S DOCKET NUMBER
10/069928	PCT/IB00/01161	BREVA 1

17. ☒ The following fees are submitted:

CALCULATIONS PTO USE ONLY

BASIC NATIONAL FEE (37 CFR §1.492 (a) (1) - (5)):

Search Report has been prepared by the EPO or JPO	$890.00
International preliminary examination fee paid to USPTO (37 CFR §1.482)	$710.00
No international preliminary examination fee paid to USPTO (37 CFR §1.482) but international search fee paid to USPTO (37 CFR §1.445(a)(2))	$740.00
Neither international preliminary examination fee (37 CFR §1.482) nor international search fee (37 CFR §1.445(a)(2)) paid to USPTO	$1040.00
International preliminary examination fee paid to USPTO (37 CFR §1.482) and all claims satisfied provisions of PCT Article 33(2)-(4)	$100.00

ENTER APPROPRIATE BASIC FEE AMOUNT =					$890.00	
Surcharge of **$130.00** for furnishing the oath or declaration later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 C.F.R. §1.492(e)).						
CLAIMS	NUMBER FILED		NUMBER EXTRA	RATE		
Total claims	20	- 20 =	0	x $ 18.00	$0.00	
Independent claims	2	- 3 =	0	x $ 84.00	$0.00	
MULTIPLE DEPENDENT CLAIM(S) (if applicable)				+ $ 280.00		
TOTAL OF ABOVE CALCULATIONS =					$890.00	
Reduction of 1/2 for filing by small entity, if applicable. A Verified Small Entity Statement must also be						
SUBTOTAL =					$890.00	
Processing fee of **$130.00** for furnishing the English translation later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 C.F.R. §1.492(f)).						
TOTAL NATIONAL FEE =					$890.00	
Fee for recording the enclosed assignment (37 C.F.R. §1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 C.F.R. §§3.28, 3.31). $40.00 per property.						
TOTAL FEES ENCLOSED =					$890.00	
					Amount to be refunded:	
					charged:	

a. ■ A check in the amount of $890.00 to cover the above fees is enclosed.

b. ☐ Please charge my Deposit Account No. 13-3402 in the amount of $ _____ to cover the above fees. A duplicate copy of this sheet is enclosed.

c. ■ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 13-3402. A duplicate copy of this sheet is enclosed.

NOTE: Where an appropriate time limit under 37 C.F.R. §§1.494 or 1.495 has not been met, a petition to revive (37 C.F.R. §1.137(a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO: Customer Number 23,599

PATENT TRADEMARK OFFICE

23599

Filed: 1 MARCH 2002

AJZ:kmo

SIGNATURE

Anthony J. Zelano

NAME

27,969

REGISTRATION NUMBER

APPLICATION DATA SHEET

APPLICATION INFORMATION

Application Type::	REGULAR
Subject Matter::	UTILITY
CD-ROM or CD-R?::	NONE
Title::	RADIOPHARMACEUTICAL PRODUCTS AND THEIR PREPARATION PROCEDURE
Attorney Docket Number::	BREVA 1

INVENTOR INFORMATION

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CORRESPONDENCE INFORMATION

Correspondence Customer Number:: 23599

REPRESENTATIVE INFORMATION

Representative Customer Number:: 23599

DOMESTIC PRIORITY INFORMATION

Application::	Continuity Type::	Parent Application::	Parent Filing Date::
This Application	National Stage of	PCT/IB00/01161	08/23/00

FOREIGN PRIORITY INFORMATION

Application Number:	Country::	Filing Date::	Priority Claimed::
99/10970	France	09/01/99	YES

ASSIGNMENT INFORMATION

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IN THE UNITED STATES DESIGNATED/ELECTED OFFICE

International Application No.	:	PCT/IB00/01161
International Filing Date	:	23 AUGUST 2000
Priority Date(s) Claimed	:	1 SEPTEMBER 1999
Applicant(s) (DO/EO/US)	:	BELLANDE, Emmanuel, et al

Title: RADIOPHARMACEUTICAL PRODUCTS AND THEIR PREPARATION PRODURE

PRELIMINARY AMENDMENT

Commissioner for Patents
Washington, D.C. 20231

SIR:

Although the claims were amended during the national phase, applicants request that examination be based on the original claims and this preliminary amendment is based thereon.

Prior to calculating the national fee, and prior to examination in the National Phase of the above-identified International application, please amend as follows:

IN THE CLAIMS:

4. (Amended) A radiopharmaceutical product according to Claim 1, in which the polysaccharide is chosen from among natural starch, cellulose and reticulated amyl pectin.

5. (Amended) A radiopharmaceutical product according to Claim 1, in which the microparticles have a dimension between 0.01 and100 μm.

6. (Amended) A radiopharmaceutical product according to Claim 1, in which the level of sequestering groups is from 0.1 to 50% relative to the saccharide patterns of polysaccharide.

7. (Amended) Utilisation of a radiopharmaceutical product according to Claim 1, in which the readioactive metal is ^{99m}Tc or ^{67}Ga to prepare a product intended for diagnosis.

8. (Amended) Utilisation of a radiopharmaceutical product according to Claim 1 in which the radioactive metal is rhenium-186 or 188, copper-64 or 67, yttrium 90, erbium 169 or samarium 153, to prepare a drug.

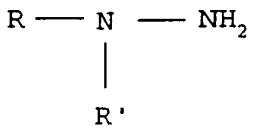
9. (Amended) Utilisation of a radiopharmaceutical product according to Claim 1, in which the radioactive metal is ^{99m}Tc to prepare a product intended for pulmonary scintigraphy.

10. (Amended) A radiopharmaceutical product according to Claim 1, under the form of a suspension of microspheres in a physiologically acceptable liquid or in lyophilised form.

11. (Amended) A procedure for preparation of a radiopharmaceutical product according to Claim 1 which comprises the following stages:

(a) submit a polysaccharide to an oxidation carried out by means of a periodate,

(b) make the oxidated polysaccharide react with a compound containing a primary amine function or hydrazin of formula $R-NH_2$ or



in which R is a hydrocarbonic or aromatic group comprising at least one atom of sulphur, in order to bond in a covalent manner to the polysaccharide with sequestering groups the metals of formulae R-NH-, R-N= or R-NH-N=, and R' is a hydrogen atom or an alkyl or methyl grouping.

(c) make the polysaccharide comprising the sequestering groups react with a salt of a radioactive metal chosen from among technetium, rhenium, copper, yttrium, erbium and samarium.

14. (Amended) A procedure according to Claim 11, in which the level of sequestering groups fixed on the polysaccharide is regulated by controlling the level of oxidation of the polysaccharide in stage (a).

17. (Amended) procedure according to Claim 10 in which the stage (c) consists of putting into contact microspheres of polysaccharide comprising sequestering groups with a solution of pertechnetate $^{99m}TcO_4^-$, in the presence of a reducing agent.

REMARKS

The purpose of this Preliminary Amendment is to eliminate multiple dependent claims in order to avoid the additional fee. Applicants reserve the right to reintroduce claims to canceled combined subject matter.

Attached hereto is a marked-up version of the changes made to the claims by the current amendment. The attached pages are captioned "**Version With Markings to Show Changes Made**".

Respectfully submitted,

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AJZ:kmo

Filed: 1 MARCH 2002

VERSION WITH MARKINGS TO SHOW CHANGES MADE

Claims 4 - 11, 14 and 17 were amended as follows:

4. (Amended) A radiopharmaceutical product according to ~~any one of~~ Claims 1 ~~to 3~~, in which the polysaccharide is chosen from among natural starch, cellulose and reticulated amyl pectin.

5. (Amended) A radiopharmaceutical product according to ~~any one of~~ Claims 1 ~~to 5~~, in which the microparticles have a dimension between 0.01 and 100 μm.

6. (Amended) A radiopharmaceutical product according to ~~any one of~~ Claims 1 ~~to 5~~, in which the level of sequestering groups is from 0.1 to 50% relative to the saccharide patterns of polysaccharide.

7. (Amended) Utilisation of a radiopharmaceutical product according to ~~any one of~~ Claims 1 ~~to 6~~, in which the readioactive metal is ^{99m}Tc or ^{67} Ga to prepare a product intended for diagnosis.

8. (Amended) Utilisation of a radiopharmaceutical product according to ~~any one of~~ Claims 1 ~~to 7~~, in which the radioactive metal is rhenium-186 or 188, copper-64 or 67, yttrium 90, erbium 169 or samarium 153, to prepare a drug.

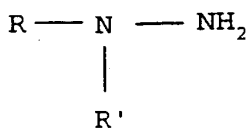
9. (Amended) Utilisation of a radiopharmaceutical product according to ~~any one of~~ Claims 1 ~~to 7~~, in which the radioactive metal is ^{99m}Tc to prepare a product intended for pulmonary scintigraphy.

10. (Amended) A radiopharmaceutical product according to ~~any one of~~ Claims 1 ~~to 6~~, under the form of a suspension of microspheres in a physiologically acceptable liquid or in lyophilised form.

11. (Amended) A procedure for preparation of a radiopharmaceutical product according to ~~any one of~~ Claims 1 ~~to 6,~~ which comprises the following stages:

(a) submit a polysaccharide to an oxidation carried out by means of a periodate,

(b) make the oxidated polysaccharide react with a compound containing a primary amine function or hydrazin of formula $R-NH_2$ or



in which R is a hydrocarbonic or aromatic group comprising at least one atom of sulphur, in order to bond in a covalent manner to the polysaccharide with sequestering groups the metals of formulae R-NH-, R-N= or R-NH-N=, and R' is a hydrogen atom or an alkyl or methyl grouping.

(c) make the polysaccharide comprising the sequestering groups react with a salt of a radioactive metal chosen from among technetium, rhenium, copper, yttrium, erbium and samarium.

14. (Amended) A procedure according to ~~any one of~~ Claims 11 ~~to 13~~, in which the level of sequestering groups fixed on the polysaccharide is regulated by controlling the level of oxidation of the polysaccharide in stage (a).

17. ~~A~~(Amended) procedure according to ~~any one of~~ Claims 10 ~~to 16,~~ in which the stage (c) consists of putting into contact microspheres of polysaccharide comprising sequestering groups with a solution of pertechnetate $^{99m}TcO_4^-$, in the presence of a reducing agent.

RADIOPHARMACEUTICAL PRODUCTS AND THEIR PREPARATION PROCEDURE

Technical field

The present invention relates to radiopharmaceutical products which can be used for diagnosis or therapy and to their preparation procedure.

In particular, it relates to radiopharmaceutical products formed for example from a suspension of particles labelled by a radioactive isotope utilisable in particular for pulmonary scintigraphy, for example in order to establish a diagnosis when a pulmonary embolism is suspected.

In this application, the products are used under the form of particles which are preferably spherical in shape and of a size ranging from 10 to 100µm. In fact, since the pulmonary capillaries have a diameter of about 7µm, the particles remain blocked in the capillaries after their intravenous injection, which makes it possible to visualise anomalies of pulmonary blood perfusion.

Evidently these products must fulfil a certain number of pharmaceutical restrictions. In particular they must have a suitable degradation rate *in vivo*, that is sufficiently slow to allow imagery to be carried out, for example by a gamma-ray camera, a minimum of about one hour, but also sufficiently rapid so as not to provoke permanent obstruction of the pulmonary capillaries, which could give rise to small thromboses. In addition, these products must not be

toxic for the organism, they must be able to be sterilised for example by autoclaving or by irradiation, they must be able to be labelled easily with a radioactive metal and be able to be packaged under the form of a stable labelling kit.

Prior Art

For example, the application for French brevet FR-A-2 273 516, deposited in 1975 by the PHARMACIA AKTIEBOLAG Company, resident in Sweden, describes the use of microspheres of ~~amyl pectin~~ amylopectin reticulated by epichlorhydrin and labelled by a simple mixture with ^{99m}Tc for pulmonary perfusion scintigraphy. These particles present several inconveniences. In fact, only the hydroxyl groupings of ~~amyl pectin~~ amylopectin used can allow this mixture labelling, and unfortunately they only form weak bonds with technetium and do not make stable labelling possible. In addition, the preparation procedure described uses many solvents and emulsifiers which are difficult to eliminate from the particles prepared. Furthermore, the exact rate of reticulation cannot be measured accurately nor controlled on this particle type.

Moreover, this document does not describe the kit compatible with routine utilisation in nuclear medicine. In fact, for an injectable preparation for humans, several manipulations such as adjunction of tin to the sterile flask, a centrifuging, a restoration of suspension, etc. are necessary, which is not compatible with sterility requirements.

Finally, the solutions obtained are not stable and the epichlorhydrin used for reticulation is recognised as being very toxic and mutagenic.

The inventors demonstrated other defects of these microparticles in the comparative examples 1 and 2 below.

The application for French brevet FR-A-2 285 857 deposited in 1975 by the PHARMAGIA FINE CHEMICALS AB Company, resident in Sweden, describes the utilisation of polysaccharide particles linked to different sequestering agents and labelled with the aid of radioactive isotopes. The particles comprise chelating groups linked by covalent bonds to which the radioactive nucleus is linked under the form of chelate type complexes which are principally composed of at least four, and preferably at least five to eight cyclic nuclei with 5 to 6 groups, enclosing the metal, and two metal-coordinating atoms. The polysaccharide is a polysaccharide reticulated chemically, for example by means of epichlorhydrin or epibromhydrin. Leaving the labelling aside, these particles present the same problems as those mentioned previously for the particles described in FR-A-2 273 516. Moreover, this document does not give any examples of labelling with technetium. Further, the labelling procedure comprises heating to 100°C in the presence of the radioactive element, a washing and a drying after labelling, which is not at all compatible with the idea of the above-mentioned labelling kit and the restrictions of sterility of usage.

Even though the labelling method described allows the particles to be labelled in a relatively stable manner, it does not make it possible to prepare a labelling kit which is pharmaceutically acceptable, in particular because it contains epichlorhydrin, and easily usable in a nuclear medicine service.

The microspheres described in these two brevet applications are thus not adapted to the pharmaceutical restrictions and they cannot be exploited. Moreover they have never been used for pulmonary scintigraphy. This type of product has been abandoned since.

The many researches carried out since 1975 for perfecting new radiopharmaceutical products have concentrated on products based on albumin-serum and its derivatives. These blood products do in fact correspond to pharmaceutical restrictions and can be used in particular for pulmonary scintigraphy. These are the products used at present in nuclear medicine.

For example, in 1975, M.A. Davis, in the document "Radiopharmaceuticals N.Y.", 1975, pages 267 to 281, described the radioactive particles intended for the study of pulmonary perfusion. The particles described in this document are macro-aggregates of radio-iodinated serum albumin (^{131}I-MAA) or microspheres of denatured human serum albumin labelled with technetium (^{99m}Tc-HAM). The microspheres of ^{99m}Tc-HAM are preferable, because of their uniformity of particle size ranging essentially between 40 and 50 µm. Moreover this document describes the general characteristics required for such radiopharmaceutical particles.

The document of R. Guiraud "Macro-aggregates and radioactive microspheres", Radiopharmaceuticals, 1997, 519, describes macro-aggregates of albumin (MAA) and microspheres of human serum albumin. It describes the labelling of such micro-aggregates and microparticles with technetium 99m by a solution of stannous chloride. It also notes that the optimum size for the microparticles is 15±5 µm. It mentions organic microspheres of starch.

At present, these macro-aggregates and microspheres of human serum albumin labelled with ^{99m}Tc are by far the most utilised in nuclear medicine. However, they present several inconveniences. For example, the variability and quality of batches of human albumin sometimes make preparation of diagnosis kits difficult, containing particles which can vary in size and number. But one of the major inconveniences is their human origin, which can pose serious problems of potential vital contamination of the type HIV, hepatitis, or Creutzfeld-Jacob disease.

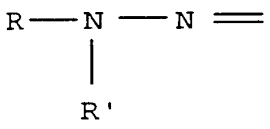
It would therefore be very interesting to be able to have microspheres labelled with ^{99m}Tc which are not of human origin in order to ensure perfect safety.

With this in view, the very recent document of A.C. Perkins, Nuclear Medicine Communications, 1999, 20, 1-3 describes ways of replacing radiopharmaceutical products obtained from blood. In particular it mentions the utilisation of recombinant materials, synthetic polymers and polypeptides. But, this document does not mention polysaccharides.

Description of the invention

The precise aim of the invention is to overcome the inconveniences mentioned above for prior art products, by providing a radiopharmaceutical product being able to be easily labelled, for example with ^{99m}Tc, presenting a very good pulmonary captation which has been demonstrated by inventors for rats, non-toxic, easily biodegradable, easily sterilisable and able to be packaged as a kit ready for labelling, stable and fulfilling the pharmaceutical restrictions for this type of product. These advantages and others will be evident from the following description.

The radiopharmaceutical product of the present invention is characterised in that it comprises a polysaccharide provided with sequestering agents linked to the polysaccharide by covalent bonds and chosen among the groups of formulae R-NH-, R-N=, and



in which R is a hydrocarbonic or aromatic group comprising at least one atom of sulphur, and R' is a hydrogen atom or an alkyl grouping, for example methyl, said sequestering groups forming a chelate type complex with a radioactive metal chosen from among technetium, rhenium, copper, yttrium, erbium, gallium and samarium.

The utilisable alkyl groups for R' can be linear or branched, and preferably they have 1 to 5 carbon atoms.

According to the invention, the polysaccharide can be soluble, or in the form of microparticles. According

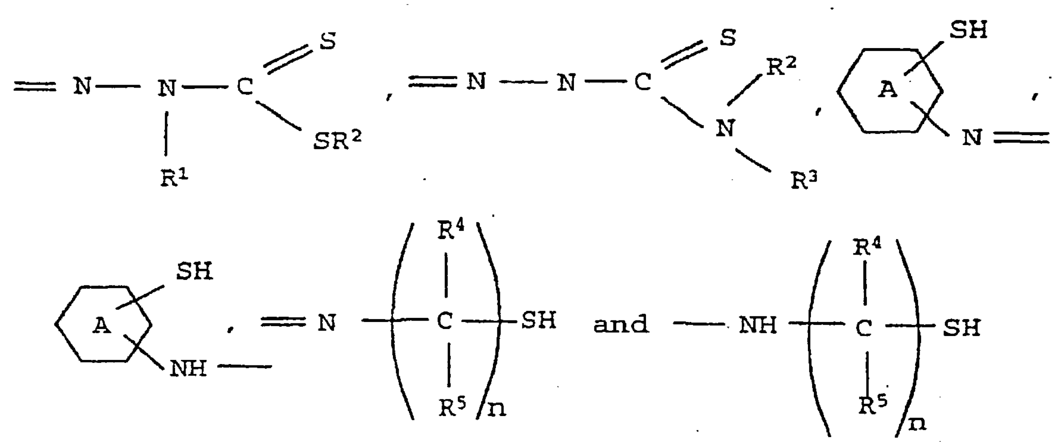
to the invention, the polysaccharide can be chosen, for example, from among natural starch, cellulose or reticulated ~~amyl pectin~~ amylopectin.

The natural starch can, for example, be maize starch.

The polysaccharide can be in the form of microparticles, for example in the form of microspheres.

The present inventors have also demonstrated that modified cellulose according to the present invention offers very good pulmonary captation and an elimination speed slower than with starch. The modified cellulose of the present invention can therefore also be used for radiotherapy, for example with labelling with rhenium, copper, or with one of the above-mentioned metals, since it corresponds to the radiotherapy necessity of using microparticles with a longer half-life.

According to the invention, the sequestering groups can be chosen for example from the groups with formulae:



starch with a base of reticulated ~~amyl pectin~~ amylopectin can thus be oxidised, then coupled to a molecule containing an amine or hydrazin function, for example S-methyl dithiocarbazate. These particles modified in this way can easily be labelled with, for example, ^{99m}Tc.

The present invention thus provides in particular microparticles prepared for example from a base of starch particles, which therefore do not present the inconveniences of the albumin mentioned above. In addition, the starch is described as an excipient in the pharmacopoeia. It is therefore easily available and at low cost.

The microparticles of the present invention also have the advantage of being able to be sterilised easily, for example by irradiation, and to be processed under the form of a kit ready for labelling.

Moreover, the present inventors have demonstrated according to the present invention that the speed of pulmonary clearance can be modified according to the level of oxidation of the microparticles used in the present invention, which is not possible, for example, with human albumin microspheres.

Another advantage of the present invention lies in the simplicity of operation of the procedure: the reaction conditions being very gentle: reactions at ambient temperature, in an aqueous medium, quasi-quantitative yields. In addition, the sequestering reactions, for example with technetium, are quantitative; they take place at room temperature and without final purification which makes it possible to adapt to the requirements of sterility and simplicity

per image. Then, manually, one defines the zones of interest in order to estimate the activity present in the different organs 15 minutes after the injection. The results are given in tables I below.

Tables I: Results

% activity 15 min. after I.V.	Example 1	Example 2	Example 3	Example 4	Example 5
% pulmon. activity	90%	85%	80%	80%	85%
% hepat. activity	<5%	<5%	<5%	<10%	<10%
pulmon. half-life	2 hours	1 hour	30 mins	2 hours	2 hours

% activity 15 min. after I.V.	Example 6	Example 7	Example 8	Example 9	~~Example 10~~ Example 13
% pulmon. activity	85%	85%	85%	85%	90%
% hepat. activity	<5%	<5%	<5%	<5%	<5%
pulmon. half-life	2 hours	2 hours	2 hours	2 hours	> 4 hours

One thus notes that the modified microspheres show very good pulmonary captation. In addition, one can modulate the speed of pulmonary elimination by varying

the oxidation level as shown in examples 1, 2 and 3 (oxidation levels 30, 20 and 10%).

The usage of cellulose makes it possible to lengthen the speed of elimination considerably (example 10, half-life > 4 hours).

Comparative example 2

In this example, natural starch is not used, but microspheres prepared from ~~amylopectin~~ amylopectin reticulated by epichlorhydrin as in the patent FR-A-2 273 516.

Part 2.1 →

Preparation of reticulated microspheres of starch

One dissolves 8 g of maize ~~amylopectin~~ amylopectin in 40 ml of a solution containing 4 g of NaOH and 0.15 g of sodium borohydride. The ~~amylopectin~~ amylopectin is left for 24 hours to dissolve. Next one prepares an emulsion by stirring 60 ml of fluid paraffin and 1.6 g of soy lecithin dissolved in 4 ml of hexane at 800 revs/min. Then one adds the aqueous phase containing the ~~amylopectin~~ amylopectin and then 3.2 ml of epichlorhydrin. The emulsion is heated to 55°C for 4 hours and then left to be stirred overnight. The microspheres obtained of a size around 50 µm are washed by 3 times 250 ml of acetone, dried and then lyophilised.

Labelling with ^{99m}Tc

One proceeds as for example 1 but using 1 mg of $SnCl_2$, $2H_2O$. The RCP is 90%.

Part 2.2 →

Starch modification

One proceeds as for example 1 but using 10 g of microspheres of ~~amylopectin~~ amylopectin reticulated by the epichlorhydrin previously prepared. One thus obtains 10 g of microspheres of amylopectin oxidised at 30% and coupled to the DTCZ at 7%.

Labelling reaction with ^{99m}Tc

One proceeds as for example 1. The RCP is 99%.

Example 15

One follows the same operational mode as in example 14 to test the microspheres of reticulated ~~amylo-~~ amylo-pectin labelled with ^{99m}Tc of the comparative example 2. The results obtained are given in table II below.

Table II

% activity 15 min. after I.V.	~~Comparative example 2~~ *	~~Example 17~~ **
% pulmonary activity	< 10%	85%
% hepatic activity	70%	<5%
pulmonary half-life	-	2 hours

One notes that contrary to the description in FR-A-2 273 516 the microspheres of reticulated ~~amylo pectin~~ amylopectin not modified chemically are labelled by ^{99m}Tc but do not present any pulmonary captation, doubtless due to the weak link between ^{99m}Tc and the microspheres. On the other hand, these microspheres transformed chemically by the procedure of the invention demonstrate good pulmonary captation.

Example 16

Starch microspheres prepared as in example 1 (starch oxidised at 30%, coupled with DTCZ at 7%) are used to produce sterile labelling kits and are ready for labelling with ^{99m}Tc.

Sterilisation of the microspheres

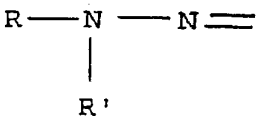
10 g of microspheres are introduced into a flask crimped and then irradiated by a source of cobalt-60.

* Comparative example 2 Part 2.1

** Comparative example 2 Part 2.2

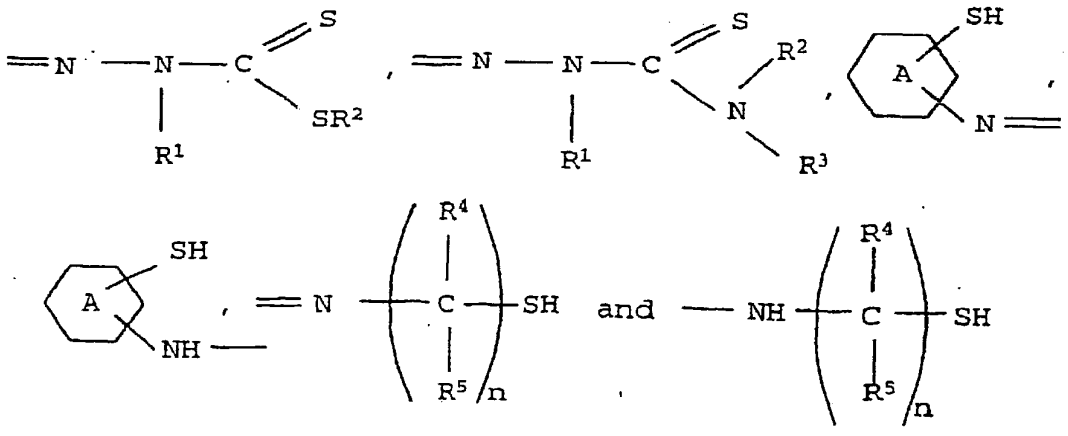
CLAIMS

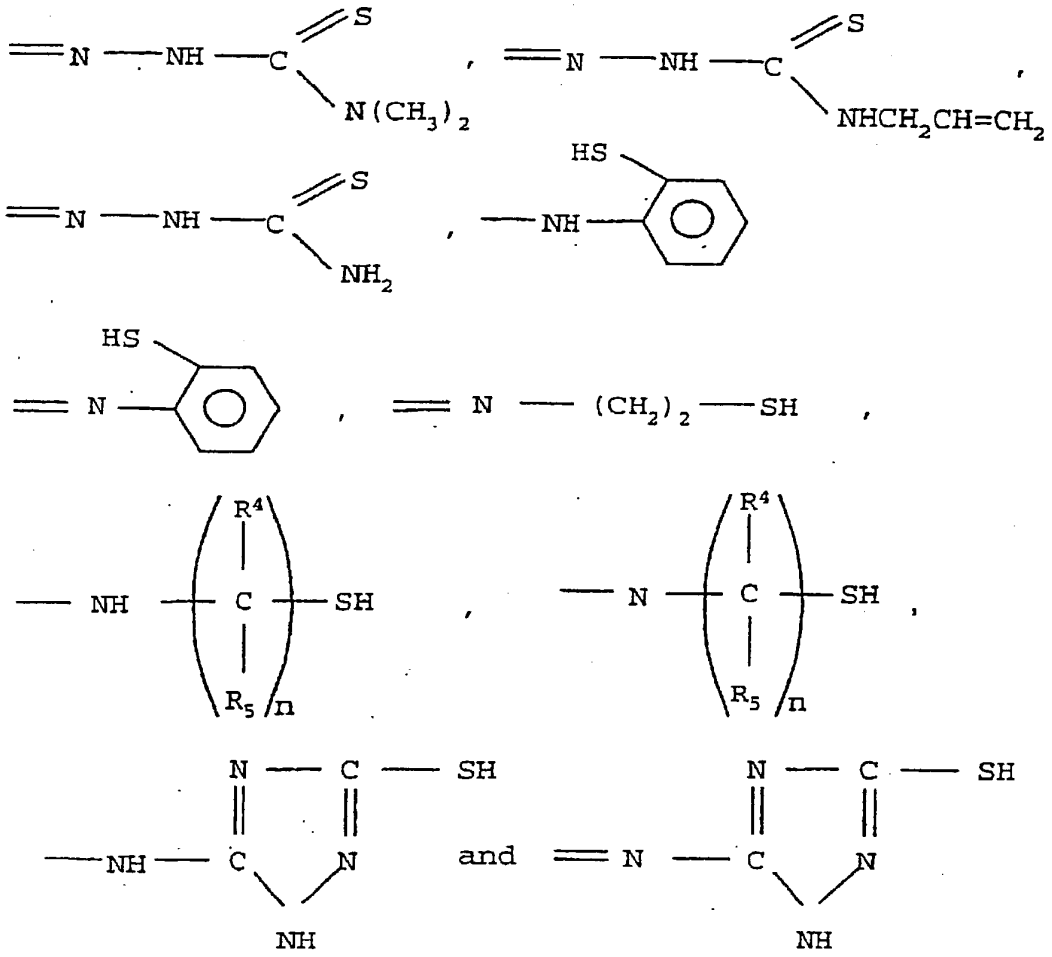
1. A radiopharmaceutical product comprising a polysaccharide provided with sequestering groups linked to the polysaccharide by covalent bonds and chosen from among the groups of formulae R-NH-, R-N=, and



in which R is a hydrocarbonic or aromatic group comprising at least one atom of sulphur, and R' is an atom of hydrogen or an alkyl or methyl grouping, said sequestering groups forming, together with a radioactive metal chosen from among technetium, rhenium, copper, yttrium, erbium, gallium and samarium, a complex of the chelate type, in which the polysaccharide is in the form of microparticles.

2. A radiopharmaceutical product according to Claim 1 in which the sequestering groups are chosen from among the groups of formulae:





and

4. A radiopharmaceutical product according to any one of Claims 1 to 3, in which the polysaccharide is chosen from among natural starch, cellulose and reticulated ~~amyl pectin~~ amylopectin.

5. A radiopharmaceutical product according to any one of Claims 1 to 5, in which the microparticles have a dimension between 0.01 and 100 µm

6. A radiopharmaceutical product according to any one of Claims 1 to 5, in which the level of

sequestering groups is from 0.1 to 50% relative to the saccharide patterns of polysaccharide.

8 X. Utilisation of a radiopharmaceutical product according to any one of Claims 1 to 6, in which the radioactive metal is ^{99m}Tc or ^{67}Ga to prepare a product intended for diagnosis.

9 X. Utilisation of a radiopharmaceutical product according to any one of Claims 1 to 6, in which the radioactive metal is rhenium-186 or 188, copper-64 or 67, yttrium 90, erbium 169 or samarium 153, to prepare a drug.

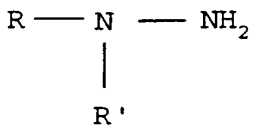
10 X. Utilisation of a radiopharmaceutical product according to any one of Claims 1 to 6, in which the radioactive metal is ^{99m}Tc to prepare a product intended for pulmonary scintigraphy.

7. X. A radiopharmaceutical product according to any one of Claims 1 to 6, under the form of a suspension of microspheres in a physiologically acceptable liquid or in lyophilised form.

11. A procedure for preparation of a radiopharmaceutical product according to any one of Claims 1 to 6, which comprises the following stages:

(a) submit a polysaccharide to an oxidation carried out by means of a periodate,

(b) make the oxidated polysaccharide react with a compound containing a primary amine function or hydrazin of formula $R-NH_2$ or

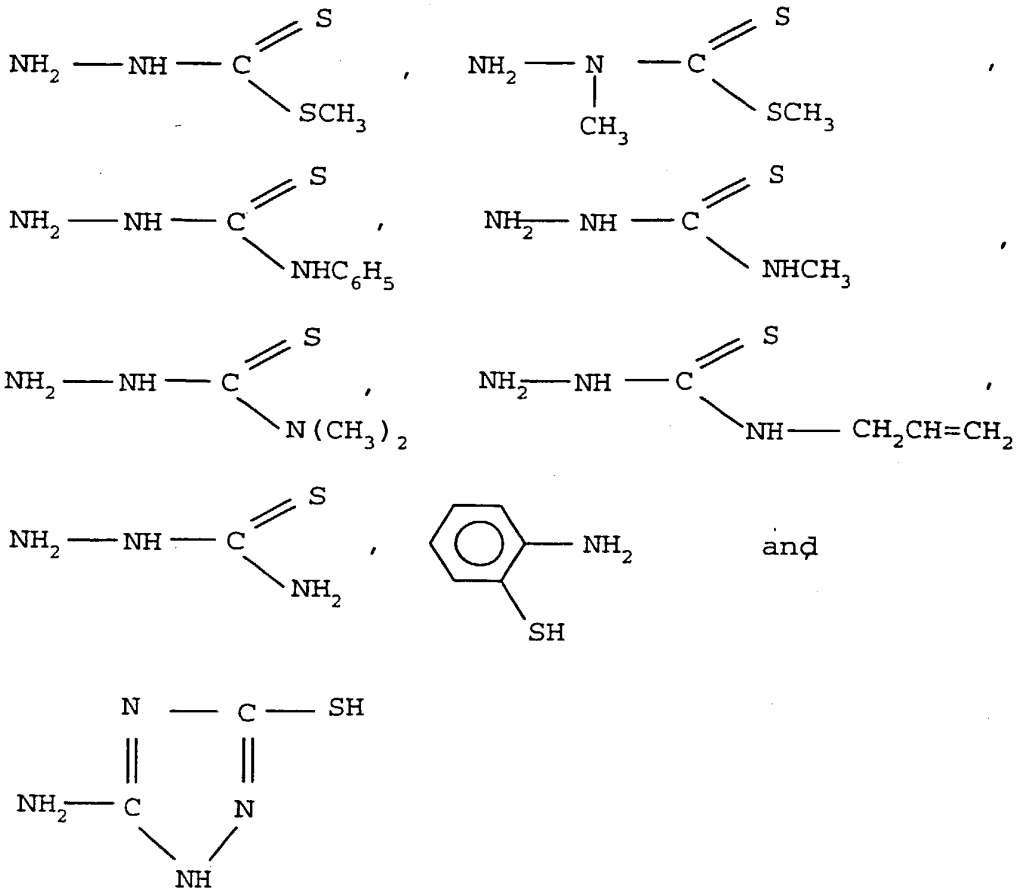


in which R is a hydrocarbonic or aromatic group comprising at least one atom of sulphur, in order to bond in a covalent manner to the polysaccharide with sequestering groups the metals of formulae R-NH-, R-N= or R-NH-N=, and R' is a hydrogen atom or an alkyl or methyl grouping.

(c) make the polysaccharide comprising the sequestering groups react with a salt of a radioactive metal chosen from among technetium, rhenium, copper, yttrium, erbium and samarium.

12. A procedure according to Claim 11, in which the compound containing a primary amine function corresponds to the formula $NH_2-(CH_2)n-SH$ with n being a whole number from 1 to 5, and comprising a supplementary stage of reduction of this compound by sodium borohydride between stages (b) and (c).

13. A procedure according to Claim 11, in which the compound bonded to the oxidised polysaccharide corresponds to one of the following formulae:



14. A procedure according to any one of Claims 11 to 13, in which the level of sequestering groups fixed on the polysaccharide is regulated by controlling the level of oxidation of the polysaccharide in stage (a).

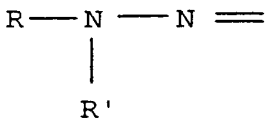
15. A procedure according to Claim 14, in which the oxidation level of the polysaccharide is from 10 to 50%.

16. A procedure according to Claim 14, in which the level of sequestering groups is from 2 to 15%.

17. A procedure according to any one of Claims 10 to 16, in which the stage (c) consists of putting into contact microspheres of polysaccharide comprising sequestering groups with a solution of pertechnetate $^{99m}TcO_4^-$, in the presence of a reducing agent.

18. A diagnosis kit which can be used for pulmonary scintigraphy which comprises:

a first flask containing a polysaccharide provided with sequestering groups linked to said polysaccharide by covalent bonds and chosen among the formulae groups R-NH-, R-N= and



in which R is a hydrocarbonic or aromatic group comprising at least one atom of sulphur, and in which R' is an atom of hydrogen or an alkyl or methyl grouping, in which the polysaccharide is in the form of lyophilised microparticles or in suspension in a pharmaceutically acceptable liquid.

19. A kit according to Claim 18 comprising also a second flask containing stannous chloride in lyophilised form.

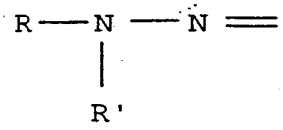
20. A kit according to Claim 18, in which the polysaccharide being in the form of lyophilised

microparticles in the first flask, said first flask also contains lyophilised stannous chloride.

ABSTRACT OF THE DISCLOSURE

The present invention relates to radiopharmaceutical products and their preparation procedure. These products can be used for pulmonary scintigraphy or for therapy.

They comprise a polysaccharide and sequestering groups of formulae R-NH-, R-N=, and



in which R is a hydrocarbonic or aromatic group comprising at least one atom of sulphur, and R' is an atom of hydrogen or an alkyl grouping such as methyl, said sequestering groups forming a chelate type complex with a radioactive metal such as technetium.

COMBINED DECLARATION FOR PATENT APPLICATION AND POWER OF ATTORNEY
(Includes Reference to PCT International Applications)

ATTORNEY'S DOCKET NUMBER

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

RADIOPHARMACEUTICAL PRODUCTS AND THEIR PREPARATION PROCEDURE.

the specification of which (check only one item below):

☐ is attached hereto.

☐ was filed as United States application

Serial No. _____

on _____

and was amended

on _____ (if applicable).

☒ was filed as PCT international application

Number PCT/IB00/01161

on August 23, 2000,

and was amended under PCT Article 19

on October 23, 2001 (if applicable).

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR § 1.56, including for continuation-in-part applications, material information which became available between the filing date of the prior application and the national or PCT international filing date of the continuation-in-part application.

I hereby claim priority benefits under Title 35, United States Code, § 119 or 365 (b) of the following United States provisional application(s) and of any foreign application(s) for patent or inventor's certificate or 365(a) of any PCT international application(s) designating at least one country other than the United States of America listed below and have also identified below any foreign application(s) for patent or inventor's certificate or any PCT international application(s) designating at least one country other than the United States of America filed by me on the same subject matter having a filing date before that of the application(s) of which priority is claimed:

PRIOR U.S. PROVISIONAL AND FOREIGN/PCT APPLICATION(S) AND ANY PRIORITY CLAIMS UNDER 35 U.S.C. 119:

COUNTRY (if PCT, indicate "PCT")	APPLICATION NUMBER	DATE OF FILING (day, month, year)	PRIORITY CLAIMED UNDER 35 USC 119
FRANCE	99 10970	01 september 1999	☒ YES ☐ NO
			☐ YES ☐ NO
			☐ YES ☐ NO
			☐ YES ☐ NO
			☐ YES ☐ NO

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PATENT TRADEMARK OFFICE

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	POST OFFICE ADDRESS	STREET	CITY	STATE & ZIP CODE/COUNTRY
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SIGNATURE OF INVENTOR 201 E. Bellande	DATE	SIGNATURE OF INVENTOR 207	DATE
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SIGNATURE OF INVENTOR 203 B. Denizot	DATE 15/02/02	SIGNATURE OF INVENTOR 209	DATE
SIGNATURE OF INVENTOR 204	DATE	SIGNATURE OF INVENTOR 210	DATE
SIGNATURE OF INVENTOR 205	DATE	SIGNATURE OF INVENTOR 211	DATE
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